American Journal of Industrial Medicine 16:631–643 (1989)

Lymphatic and Hematopoietic Tissue Cancer in a Chemical Manufacturing Environment

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Nested case-control studies of non-Hodgkin's lymphoma (52 cases), multiple myeloma (20 cases), nonlymphocytic leukemia (39 cases), and lymphocytic leukemia (18 cases) were conducted within a cohort of employed men from two chemical manufacturing facilities and a research and development center. Exposure odds ratios were examined in relation to 111 work areas, 21 specific chemicals, and 52 chemical activity groups. Associations were observed for a maintenance and construction subgroup (non-Hodgkin's lymphoma) and a chlorohydrin production unit (nonlymphocytic leukemia). The odds ratio for the association of "foremen and others" with non-Hodgkin's lymphoma was 3.2 (CI_{95} = 1.47–7.2) based on 11 cases. A duration-response trend was observed for the chlorohydrin unit with three of four cases assigned 5+ years to that unit. An association between non-Hodgkin's lymphoma and assignment to strong acid alcohol production units (OR = 8.3; CI_{95} = 2.3–30.7) was not supported by a duration-response trend. Two highly correlated chemical groups, antioxidants (five cases) and nitriles (four cases), were over-represented among multiple myeloma cases. A duration effect was observed. However, examination of work histories did not reveal common jobs or departments among these cases.

Key words: leukemia, lymphoma, multiple myeloma, occupational epidemiology, alkyl sulfates, ethylene chlorohydrin

INTRODUCTION

A recently completed cohort mortality study of 29,139 men employed in two large Union Carbide Corporation (UCC) chemical manufacturing facilities and a research and development center identified an increase in deaths caused by lymphatic and hematopoietic tissue cancer [Rinsky et al., 1988]. These findings led to the initiation of concurrent case-control studies of four distinct subcategories of lymphatic and hematopoietic tissue cancers: non-Hodgkin's lymphoma, multiple myeloma, lymphocytic leukemia, and nonlymphocytic leukemia. Hodgkin's disease was not included as a subcategory of interest because of an observed deficit in deaths from this cause (Standardized Mortality Ratio (SMR) = 53) [Rinsky et al., 1988].

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Accepted for publication June 5, 1989.

The etiologic profiles of these relatively uncommon cancers are unique, but there are also many shared risk factors. Death rates for all of these cancers appear to increase with higher socioeconomic status [Blattner, 1982; Greene, 1982; Heath, 1982]. Ionizing radiation has been identified as a positive risk factor for leukemias other than chronic lymphocytic leukemia and for multiple myeloma and as a likely risk factor for non-Hodgkin's lymphoma [Upton, 1984]. Among individuals with genetically determined immunodeficiency diseases who subsequently develop malignancies, non-Hodgkin's lymphoma and lymphoid leukemias represent the dominant tumor histology [Spector et al., 1978]. Non-Hodgkin's lymphoma has also been strongly associated with acquired immunosuppression [Hoover and Fraumeni, 1973].

Although occupational associations have been identified by industry and within job classifications for these diseases, few relationships with specific industrial chemicals have been established. Myelogenous leukemia has been etiologically linked to benzene, and associations between benzene and multiple myeloma have been suggested [Rinsky et al., 1987]. Exposure to ethylene oxide has also been associated with leukemia occurrence [Hogstedt et al., 1986]. Inconsistent increases of lymphatic and hematopoietic tissue cancers have been reported among workers potentially exposed to butadiene [Meinhardt et al., 1982; Downs et al., 1987; Matanoski et al., 1988a,b].

MATERIALS AND METHODS

Cases were identified from a review of both underlying and contributory causes of death among male decedents (1940–1978) from the cohort study. The death certificate diagnosis was accepted as the basis for classifying all cases. Although some misclassification of disease status would be expected using death certificate diagnoses, the agreement between death certification and tumor registry diagnoses has been reported to be above average for leukemia and multiple myeloma and average for non-Hodgkin's lymphoma compared with that for other cancer sites (Percy et al., 1981). Misclassification between the two subcategories of leukemia would be expected to pose more of a potential problem. The general effect of misclassification is to diminish the chances of detecting etiologic relationships in the data. The case series was restricted to men when only four lymphatic or hematopoietic tissue neoplasms were found among former women employees and because of incomplete follow-up among women employees. Vital status follow-up was complete for 96% of the 29,139 men in the cohort study. Controls were selected from the total employee cohort according to a group-matched incidence density sampling design described by Greenland and Thomas [1982]. Time from hire to death for cases was categorized into 5 year increments of survival (0–4, 5–9, . . . 35–39). Controls were randomly selected with replacement in a 5:1 ratio to cases such that they were first employed in the same decade and survived at least to the start of the same 5 year survival period as cases. For example, cases hired in the 1950s who survived 20–24 years (survival interval) were frequency matched to men hired in the 1950s who survived at least 20 years as well. Frequency-matched controls were independently selected in this manner for each of the individual disease subcategories to be examined. For both cases and controls, the employee's job history was evaluated up to the start of the same 5 year survival interval.

The assessment of potential workplace exposures has been described in a separate report [Ott et al., 1989]. The first step was to subdivide all work activities into

six major categories: 1) administrative and business services; 2) construction; 3) maintenance; 4) production support services; 5) research and development; and 6) production. Using departmental and job assignment records and historical information regarding process dates and descriptions from 1925 through 1978, a further subdivision of all work activities into 111 distinct and mutually exclusive work areas (83 production work areas and 28 nonproduction work activities) was made. Exposure to each work area or activity was based on the work history information for each study subject and was truncated for both cases and controls at the beginning of the survival interval of the cases.

For production work areas, 1,020 substances were identified as having been used or produced in one or more of the production units over the 54 year history (1925–1978) of the facilities. Twenty-one of these substances, designated "suspect" substances, were selected for specific analysis based on carcinogenic potential considerations (evidence of carcinogenicity or mutagenicity) and the use of these materials in multiple work areas [Soderman, 1982; Fishbein, 1979]. Of the 1,020 identified chemical agents, 598 were present in only one work area and hence were adequately covered through the work area analyses.

Potential employee contact with a specific substance was determined by tracing each employee's work assignments and linking these assignment records to a separate computer file that contained a history of departmental usage for each substance. Therefore, assignment to a departmental unit implied potential exposure to any chemical in use during the time period of an employee's assignment to that unit.

Additionally, all chemicals were categorized into 52 chemical groups according to chemical structure or, in some cases, according to the identified use of the material. Twenty groups of notable concern from a carcinogenic standpoint including epoxides, various halogenated compounds, fused cyclics, nitriles, and vinylics were selected as "suspect" chemical groups, although analyses were conducted for all 52 groups. Potential exposure to each chemical group was assumed on the basis of assignment to a production unit with a history of usage of any member of that chemical group.

Initial data analysis included crude odds ratio (OR) calculations for each exposure measure classified on an ever/never basis and for each of the four disease categories. Ever exposed implies that the employee worked for 1 or more days with the chemical or in the specified work area. Unconditional analyses were employed since there was no individual matching of the cases to controls. ORs were also examined initially for 1) the six major work areas and all 21 selected chemicals combined and 2) the 111 work areas and each selected chemical for all case groups combined. These were not informative beyond what was seen based on the other exposure measures and are therefore not presented here. Stratified examination of odds ratios was conducted to assess duration of exposure effects when the crude odds ratios were 1.3 or greater and there were four or more exposed cases. Duration was categorized as none, <5 years, and $5+$ years.

Analyses were also conducted using a 5 year exposure lag under the assumption that exposures that occurred close to the time of death might be unrelated to the outcome. In these analyses, crude odds ratios were recalculated excluding exposures for cases and controls that occurred 5 years or less from the beginning of the case survival interval. Since cases died at any time within the 5 year interval, the lag period effectively ranged from 5 to 9 years, with an average of about 7 years.

TABLE I. Exposure Odds Ratios by Ever/Never Classification of Having Been Employed in Selected Work Areas for Each Disease Category Among Male Employees at Three UCC Facilities, 1940–1978*

	Disease subcategory							
	Non-Hodgkin's lymphoma		Multiple myeloma		Leukemia			
					Nonlymphocytic		Lymphocytic	
Work area	OR	No. of cases	OR	No. of cases	OR	No. of cases	OR	No. of cases
Plant support services	0.7	10	1.4	8	1.6	12	2.6	8
Business services	1.9	3						
Utilities	1.4	3						
Engineering	1.1	4						
Research and development	0.5	3	1.6	3	1.4	6		
Research laboratories					1.7	3		
Ethanol unit	5.4[a]	5						
Chlorohydrin unit					3.1	4		
Vinylite solvent resins	1.7	3						
Olefins unit			1.8	3				
Materials distribution	0.9	7			0.7	3		
Maintenance and construction								
Laborers	1.1	13	0.6	6	0.7	8	1.1	5
Foreman and others	3.2[a]	11	1.6	3	1.9	6	2.9	4
Carpenters	1.5	3			1.3	3		
Pipefitters	1.4	4			1.8	5		
Insulators	2.2	3						
Repairmen/millwrights					1.9	3		
Welder/metal worker	0.9	4					1.8	3
Instrument men	5.2[a]	3						
Riggers	3.9	3						

*Includes all work areas with at least three cases for one or more of the disease subcategories, based on an examination of 111 total work areas.
[a]Lower 95% confidence limit exceeds 1.0.

Age-adjusted stratified analyses, which were also conducted, did not materially modify the odds ratio estimates. The unadjusted estimates are therefore presented.

RESULTS

There were 129 lymphatic or hematopoietic tissue malignancies excluding Hodgkin's disease identified in the years between 1940 and 1978. These were distributed as 52 cases of non-Hodgkin's lymphoma, 20 cases of multiple myeloma, 39 cases of nonlymphocytic leukemia, and 18 cases of lymphocytic leukemia. Most cases had been hired before or during the 1940s. Interval between hire date or January 1, 1940, and date of death was shortest for nonlymphocytic leukemia cases and longest for multiple myeloma cases. Average age at death was lowest for nonlymphocytic leukemia cases (55.1 years) and non-Hodgkin's lymphoma (56.0 years) and was highest for lymphocytic leukemia (63.7 years).

Work Areas

ORs were examined for the 111 work areas. Results are presented in Table I for those with three or more exposed cases. In these analyses, maintenance and con-

TABLE II. Exposure Odds Ratios by Length of Time Having Been Employed in Selected Work Areas for Each Disease Subcategory Among Male Employees at Three UCC Facilities, 1940–1978*

Work area	Disease subcategory[a]	Duration of work (years)				
		0	<5		5+	
		OR	OR	No. of cases	OR	No. of cases
Plant support services	MM	1.0	1.2	6	3.8	2
	NLL	1.0	1.2	8	3.8	4
	LL	1.0	2.9	7	2.3	1
Research and development	NLL	1.0	1.0	3	2.6	3
Ethanol unit	NHL	1.0	13.6	5	0.0	0
Chlorohydrin unit	NLL	1.0	0.9	1	16.1	3
Maintenance and construction						
Foremen and others	NHL	1.0	3.5	6	2.9	5
	NLL	1.0	0.7	1	2.7	5
	LL	1.0	3.9	2	2.3	2
Pipefitters	NHL	1.0	1.9	4	0.0	0
	NLL	1.0	2.1	4	1.1	1

*Results computed only for work areas and disease subcategories for which the exposure odds ratio was 1.3 or greater and there were at least four exposed cases.
[a]MM, multiple myeloma; NLL, nonlymphocytic leukemia; LL, lymphocytic leukemia; NHL, non-Hodgkins lymphoma.

struction personnel were combined and grouped according to common trades. Elevated ORs were observed in the ethanol unit (OR = 5.4; 95% confidence interval [CI_{95} = 1.5–19.5) and two maintenance and construction groups, "foremen and others" (OR = 3.2; CI_{95} = 1.4–7.2), and instrument men (OR = 5.2; CI_{95} = 1.0–26.7), for non-Hodgkin's lymphoma. With the exposure lag, the OR for instrument men and non-Hodgkin's lymphoma increased to 7.9.

An association with long duration of assignment in the chlorohydrin unit was observed for nonlymphocytic leukemia. Three of the four cases worked more than 5 years; one worked less than 5 years. The crude OR for this association was 3.1 (CI_{95} = 0.9–11.0) and increased to 3.6 with the lagged exposure.

There was no apparent association between length of employment in the ethanol unit and non-Hodgkin's lymphoma. The OR for those assigned less than 5 years to this unit was 13.6. Three of the five cases had worked for two months or less, and no case and three controls worked 5 years or more in the unit.

The OR was 3.5 for non-Hodgkin's lymphoma and "foremen and others" assigned less than 5 years (Table II). It was 2.9 for those with this assignment 5 years or more. Review of the work histories for the long duration cases did not reveal a common pattern of job assignment. The group included a general shop foreman, a leadburner foreman, a rigger foreman, a construction supervisor, and a warehouseman.

Suspect Chemicals

Exposure odds ratios are presented in Table III for the selected suspect chemicals that were present in multiple work areas. Many of the comparisons were based on fewer than three exposed cases. Although none of the lower 95% confidence limits

TABLE III. Exposure Odds Ratios by Ever/Never Classification of Having Worked With 21 Selected Chemicals for Each Disease Subcategory Among Male Employees at Three UCC Facilities, 1940–1978

	Disease subcategory							
	Non-Hodgkin's lymphoma		Multiple myeloma		Leukemia			
					Nonlymphocytic		Lymphocytic	
Chemical	OR	No. of cases	OR	No. of cases	OR	No. of cases	OR	No. of cases
Acetaldehyde	2.5	7	2.3	3	1.3	3		0
Acetonitrile	5.2	2			2.5	1		0
Acrolein	2.6	2	1.7	1	2.6	3		0
Acrylonitrile	2.5	6	2.0	3	0.4	1	2.6	1
Allyl alcohol	2.6	2	2.6	1	2.5	1		0
Allyl chloride	1.7	1	5.2	1	2.6	2		0
Benzene	1.0	5	1.4	5	1.0	5	1.5	2
Butadiene	0.7	3	1.4	3	1.4	3	1.5	2
Butylene oxide		0	–[a]	1	5.1	1		0
Dichloroethyl ether	0.8	2	2.6	1	2.2	5		0
Dioxane	1.3	1		0	2.6	3		0
Epichlorohydrin	1.7	1	11.0	2	3.5	2		0
Ethylene chlorohydrin	0.4	1	2.6	1	2.7	5		0
Ethylene dichloride	0.3	1		0	1.9	5		0
Ethylene oxide	0.7	3	2.1	2	2.3	7		0
Formaldehyde	2.0	2	1.0	1	2.6	2	2.6	1
Ketene	1.3	1	2.6	1	1.7	1		0
Propylene oxide	1.5	4	3.4	3	1.3	3		0
Styrene	2.0	2	1.0	1	1.0	1	5.2	1
Vinyl acetate	1.2	7	1.6	3	0.5	2	1.8	2
Vinyl chloride	1.7	6	0.8	1	0.3	1	1.3	1

[a]Indeterminate.

exceeded 1.0, there were nine comparisons with ORs of 1.3 or greater and with four or more exposed cases. For each of these comparisons, a subanalysis by duration of exposure was performed (Table IV). The ORs for ethylene dichloride and nonlymphocytic leukemia exhibited a duration-response trend with ORs of 0.5 in the <5 years and 7.1 in the 5+ years duration categories.

Since groups of chemicals tend to be used together in chemical processes, assignment to a process unit implies potential exposure to all involved chemicals. Analyses for dichloroethyl ether, ethylene oxide, and ethylene chlorohydrin were highly confounded since five cases of nonlymphocytic leukemia experienced exposures to all three substances. Four of these cases had been exposed to these substances as well as to ethylene dichloride through their assignments to the chlorohydrin unit previously examined in the work area analyses. Positive associations were suggested between duration of contact with each of these substances and nonlymphocytic leukemia, although the evidence was not as strong as the duration pattern seen for the chlorohydrin unit.

The patterns of ORs and duration trends for acetaldehyde and acrylonitrile and non-Hodgkin's lymphoma were also similar because of concomitant usage of these two chemicals. The ORs for associations between these cancer types and 1,3-butadiene exposure were 0.7 (three cases) for non-Hodgkin's lymphoma, 1.4 (three cases)

TABLE IV. Exposure Odds Ratios by Length of Time Having Worked With Selected Chemicals for Each Disease Subcategory Among Male Employees at Three UCC Facilities, 1940–1978*

Chemical	Disease subcategory[b]	Duration of Exposure (years)[a]				
		0	<5		5+	
		OR	OR	No. of cases	OR	No. of cases
Acetaldehyde	NHL	1.0	3.3	6	1.1	1
Acrylonitrile	NHL	1.0	3.8	5	0.9	1
Benzene	MM	1.0	1.2	2	1.6	3
Dichloroethyl ether	NLL	1.0	1.3	2	4.0	3
Ethylene chlorohydrin	NLL	1.0	2.2	2	3.3	3
Ethylene dichloride	NLL	1.0	0.5	1	7.1	4
Ethylene oxide	NLL	1.0	2.1	3	2.5	4
Propylene oxide	NHL	1.0	1.7	2	1.3	2
Vinyl chloride	NHL	1.0	1.7	4	1.5	2

*Results computed only for chemicals and disease subcategories for which the crude exposure odds ratio was 1.3 or greater and there were at least four exposed cases.
[a]Odds ratios calculated relative to the nonexposed group.
[b]See Table II.

for multiple myeloma, 1.4 (three cases) for nonlymphocytic leukemia, and 1.5 (two cases) for lymphocytic leukemia. Duration of assignment patterns of the cases were unremarkable.

Chemical Groups

Odds ratios are provided in Table V for the suspect chemical groups with at least three exposed cases in one or more disease subcategories. Several positive associations were identified. Statistically significant ORs were observed for non-Hodgkin's lymphoma and alkyl sulfates (OR = 5.1) based on eight exposed cases and for metal salts of high toxicity (OR = 2.2) based on ten exposed cases. The latter association did not exhibit a trend with duration and diminished to a nonsignificant OR of 1.8 when a 5 year lag in calculating exposure duration was applied. The number of exposed cases decreased from ten to eight because of the loss of two cases first exposed to metal salts of high toxicity within 5 years of the start of the interval of their death.

The association of alkyl sulfates with non-Hodgkin's lymphoma persisted with the 5 year lag in exposure duration but demonstrated a negative trend with duration of exposure (Table VI). Only one exposed case, as opposed to four exposed controls, worked with alkyl sulfates for 5 years or more. One case was potentially exposed to dimethyl sulfate for several years. The seven remaining cases had been exposed to other alkyl sulfates mainly because of assignments in the ethanol and isopropanol units. An association between employment in the ethanol unit and non-Hodgkin's lymphoma in the absence of a positive trend with duration was reported earlier in the work areas analyses.

Two other chemical groups examined in the stratified analyses produced apparent trends with duration of exposure. These were antioxidants and nitriles, which were associated with multiple myeloma. There were nonstatistically significant ORs for these comparisons (3.4 and 3.3), based on five and four cases, respectively. There

TABLE V. Exposure Odds Ratios by Ever/Never Classification of Having Worked With 20 Suspect Chemical Functional Groups for Each Disease Subcategory Among Male Employees at Three UCC Facilities, 1940–1978

	Disease subcategory							
	Non-Hodgkin's lymphoma		Multiple myeloma		Leukemia			
					Nonlymphocytic		Lymphocytic	
Suspect chemical group	OR	No. of cases	OR	No. of cases	OR	No. of cases	OR	No. of cases
Acrylates	0.9	2	2.3	3	1.7	2	1.7	1
Aldehydes saturated	1.3	7	2.3	4	1.7	6	0.6	1
Aldehydes unsaturated	1.0	4	2.3	4	1.6	5	0.8	1
Alkenes	1.7	11	1.5	5	1.5	9	0.8	2
Alkyl sulfates	5.1[a]	8	1.7	1		0		0
Alkylene amines	1.3	3	2.1	2	0.5	1		0
Anhydrides	2.0	6	1.7	2	1.1	4	1.5	2
Antioxidants	1.3	5	3.4	5	1.8	5	0.7	1
Aryls	0.8	5	1.2	5	1.2	6	0.9	2
Epoxides	1.0	5	1.8	3	1.8	7	1.3	1
Fused cyclics	2.1	4	0.7	1	0.9	2	1.7	1
Haloalkanes	1.1	6	1.5	2	1.7	8	3.6	2
Haloaryls	1.7	2	5.2	1	1.3	1		0
Haloethers	0.8	2	1.7	1	2.2	5		0
Metal salts, high tox.	2.2[a]	10	0.9	2	0.9	4	0.8	1
Nitriles	1.9	4	3.3	4	2.1	2	1.3	1
Peroxides	2.1	7	0.7	1	0.5	2	3.6	2
Phthalates	1.7	2		0	1.7	1	—[b]	1
Pyridines	1.7	2	5.4	2	0.6	1		
Vinylics	1.1	10	1.6	7	1.0	7	0.9	3

[a]Lower 95% confidence limit exceeds 1.0.
[b]Indeterminate.

was a high correlation between individuals exposed to nitriles and those exposed to antioxidants. Nine of the 14 persons with antioxidant exposure were also exposed to nitriles. Examination of work histories of these cases did not suggest any common jobs, departments, or specific chemicals within these chemical groups.

Among non-suspect chemical functional groups, there was a statistically significant OR associating nonlymphocytic leukemia and the halohydrins (OR = 3.0). This observation reflects the association seen in the chlorohydrin unit and for ethylene chlorohydrin, the primary chemical making up the halohydrin group.

DISCUSSION

This research is characterized by the familiar problem of diminishing cell sizes as both exposure and health outcome categories are delineated with greater specificity [Sokas, 1986]. The problem occurs despite the relatively large employee population under surveillance because the specific endpoints are relatively uncommon events and because of the diversity of the exposures in this chemical manufacturing environment.

The conduct of the research is further complicated by differing levels of knowledge regarding exposure across the various work areas and by the overlapping nature of exposures that have occurred. As a consequence of the exposure assignment

TABLE VI. Exposure Odds Ratios by Years of Having Worked With 20 Suspect Chemical Functional Groups for Each Disease Subcategory Among Male Employees at Three UCC Facilities, 1940–1978*

Suspect chemical group	Disease subcategory[b]	Duration of exposure (years)[a]				
		0	<5		5+	
		OR	OR	No. of cases	OR	No. of cases
Aldehydes sat.	NHL	1.0	1.8	5	0.8	2
	MM	1.0	1.6	2	3.8	2
	NLL	1.0	2.0	3	1.5	3
Aldehydes unsat.	MM	1.0	1.3	2	11.3	2
	NLL	1.0	1.8	3	1.5	2
Alkenes	NHL	1.0	2.4	7	1.2	4
	MM	1.0	0.9	1	1.8	4
	NLL	1.0	1.4	3	1.5	6
Alkyl sulfates	NHL	1.0	8.0	7	1.4	1
Anhydrides	NHL	1.0	1.2	2	3.3	4
Antioxidants	NHL	1.0	1.0	2	1.5	3
	MM	1.0	2.4	2	4.6	3
	NLL	1.0	2.4	4	0.9	1
Epoxides	NLL	1.0	1.6	3	2.0	4
Fused cyclics	NHL	1.0	2.1	2	2.1	2
Haloalkanes	NLL	1.0	1.5	4	2.0	4
Haloethers	NLL	1.0	1.3	2	4.0	3
Metal salts, high tox.	NHL	1.0	2.6	7	1.7	3
Nitriles	NHL	1.0	2.6	3	1.0	1
	MM	1.0	0.8	1	39.7	3
Peroxides	NHL	1.0	2.4	4	1.8	3
Vinylics	MM	1.0	1.0	2	2.2	5

*Results computed only for chemical groups and disease subcategories for which the crude exposure odds ratio was 1.3 or greater and there were at least four cases.
[a]Odds ratios calculated relative to the nonexposed group.
[b]See Table II.

methodology, an association between a production work area and a particular disease tends to produce a similar association with each of the chemicals or chemical groups used in that work area. In such circumstances, the attribution of an effect to a single agent becomes problematic. Because of the multiple comparisons made, we attempted to evaluate the internal consistency of findings by examining outcomes in relation to exposure duration and lagged exposure duration, as well as to evaluate the external consistency of our observations.

The detailed analyses across work areas, specific chemicals, and chemical groups appeared consistent with one another and drew our attention to several areas that merit further comment. For the nonproduction work activities, the findings of note relate to maintenance and construction trade groups. Elevated ORs were observed for the "foremen and others" subgroup of maintenance and construction personnel, for each of the disease subcategories. The highest OR observed was related to non-Hodgkin's lymphoma. Although this work group is heterogeneous in composition, a common trait is that many of these individuals have had long careers in maintenance and construction work culminating in assignments as foremen.

There were three cases of non-Hodgkin's lymphoma among insulators (OR =

2.2). The individual in this group with the longest history of work as an insulator died from a lymphoma of the gastrointestinal tract. This observation is consistent with a reported relationship between asbestos exposure and lymphomas of the gastrointestinal tract [Ross et al., 1982]. Riggers represent another group of employees with potential exposure to asbestos. There were three non-Hodgkin's lymphoma cases among riggers (OR = 3.9); however, none of the cases were of extranodal sites. We did not calculate lung cancer risk for riggers and insulators.

A second group of positive associations evolved from four cases of nonlymphocytic leukemia observed among chlorohydrin unit employees at the South Charleston plant. Each of these employees was first assigned to the unit during the 1930s. The ORs increased with longer duration of assignment in the unit as three of the cases had worked there for more than 5 years. These cases included an 82-year-old man who died of acute leukemia, a 62-year-old with chronic myelogenous leukemia, and a 63-year-old with acute myelogenous leukemia. Five of the 21 suspect chemicals (dichloroethyl ether, ethylene chlorohydrin, ethylene dichloride, ethylene oxide, and epichlorohydrin) had been present in the unit (all but ethylene oxide and epichlorohydrin were present throughout the history of the unit) and consequently were found to have elevated exposure ORs and suggestive trends with duration of assignment. Little information is available concerning levels of exposure to these and possibly other chemicals in the chlorohydrin unit during the years of its operation (1926 to 1972). Ethylene chlorohydrin was the most important of the suspect chemicals from a manufacturing viewpoint, being the primary product of the unit. Ethylene dichloride and dichloroethyl ether were low volume by-products, probably comprising less than 10% of the total process output. Epichlorohydrin was only present in later years. Ethylene oxide was thought to have been processed in the unit intermittently when the chlorohydrin process was shut down, and exposures to this chemical are presumed to have been low. The chlorohydrin unit findings were also analyzed and described in a cohort study of ethylene oxide workers from the same locations included in the present investigation [Greenberg et al., 1989].

A third area of suggestive findings related to work assignments in the ethanol and isopropanol strong acid processing units and non-Hodgkin's lymphoma. The exposure odds ratio for the two strong acid process units combined was 8.3 (CI_{95} = 2.3–30.7). Only one of six cases, however, worked 5 years or more in either of these units. Two of the cases had been assigned to the isopropanol unit for 1.5 months (interval between first exposure and death, 47 years) and 9 years (interval from first exposure and death, 18 years), respectively. The remaining cases were assigned to the ethanol process for periods of from 1 month to 4.5 years. Intervals between first exposure and death were from 7 to 32 years.

The data from these two processes were combined after the initial observation of a non-Hodgkin's lymphoma excess in each unit. The rationale for the combined analysis was based on the similarity of processes and families of chemicals present in the two operations. Both processes were based on the reaction of alkenes (ethylene, propylene) with concentrated sulfuric acid to form ethanol and isopropanol. Both units also formed alkyl sulfate intermediates (ethyl, diethyl, isopropyl, and diisopropyl sulfates). Consequently, there was a similarly elevated OR for the alkyl sulfates group in the chemical group analyses. Six of the eight alkyl sulfate-exposed cases had assignments to one of the strong acid units. Alkyl sulfates have been found to be carcinogenic (lung) in animals by injection [Soderman, 1982], and dimethyl sulfate

has been found to produce lymphomas and upper respiratory cancers in rats by inhalation [Soderman, 1982].

Both the ethanol and isopropanol strong acid processes have been previously associated with an increased risk of upper respiratory tract cancers in humans [Weil et al., 1952; Lynch et al., 1979]. The morbidity and mortality experience of strong acid ethanol and weak acid isopropanol unit employees at an Exxon facility revealed an excess of laryngeal cancers [Lynch et al., 1979]. Individual cases had worked in both units, but appeared to have spent more time assigned to the ethanol unit. The researchers attributed this finding to the high concentrations of diethyl sulfate formed in the strong acid process. A proportionate increase in lymphatic and hematopoietic tissue tumors was also observed, 7.0% versus 4.3% (U.S. white males), when the cohort was defined to include both process and maintenance employees at the plant. However, no further subdivision of these cancers was provided, and the differences were not judged to be statistically significant.

In a 1952 report, the UCC South Charleston isopropanol strong acid process was linked to the occurrence of upper respiratory tract tumors in active employees from 1928 to 1950 [Weil et al., 1952]. Cases of paranasal sinus cancer (four), papillomas of the vocal cords (two; one nonmalignant), and lung cancer (one) were identified among relatively young men after 7 to 14 years of continuous exposure. The principal period of exposure for these individuals was prior to 1940. These tumor occurrences were initially recognized by the plant physician. No similar findings were noted for the ethanol unit. Subsequently the isopropanol unit operation was modified to the weak acid process and was located in a new facility that used a well-ventilated remote-control booth to prevent routine contact with chemical reactants. A follow-up analysis of the long-term mortality experience of employees who worked in the strong acid ethanol and isopropanol process units is in progress.

Among other findings of interest was the weak positive association of benzene with multiple myeloma and lymphocytic leukemia, but lack of association with non-lymphocytic leukemia. No clear excess of any type of lymphatic and hematopoietic tissue cancers was seen in association with 1,3-butadiene exposure. The OR for non-Hodgkin's lymphoma was less than 1.0 and between 1.4 and 1.5 for the other three types of cancer. There were too few exposed cases, however, to draw conclusions from these data alone.

In summary, a search for commonality of "exposures" among decedents from non-Hodgkin's lymphoma, leukemia, and multiple myeloma in this large industrial cohort pointed to a maintenance and construction subgroup and to two particular work areas. Similar to other research related to maintenance and construction assignments, little specificity was possible in evaluating positive findings. The difficulty was increased in the present investigation because of the heterogeneity of the category "foremen and others."

The association between non-Hodgkin's lymphoma and the two strong acid processes combined produced a high OR in these work areas with potential exposures to alkyl sulfates. The evidence for a work-related effect was weakened by the short duration of assignment of the cases to these units. The internal consistency of a leukemia/chlorohydrin unit association appeared stronger, since it was supported by both an elevated odds ratio and a duration-response trend. However, the confounding of chemical exposures precluded attributing this finding to a specific agent. All of these units operated in the oldest of the three facilities studied and were discontinued

more than 16 years ago. The mortality experience of current and former employees at this location will continue to be monitored, with particular attention given to the relationships suggested by this investigation.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the National Institutes of Occupational Safety and Health for continual cooperation and scientific reviews. They also thank Rob Schnatter and Don Gosselin for technical assistance.

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